Rec'd PCT/PTO 23 NOV 1999

FORM PTO-1390 (Modified) (REV 10-95) U.S. DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE

TRANSMITTAL LETTER TO THE UNITED STATES DESIGNATED/ELECTED OFFICE (DO/EO/US) CONCERNING A FILING UNDER 35 U.S.C. 371

ATTORNEY'S DOCKET NUMBER	
35280047US00	
U.S. APPLICATION NO. (IF KNOWN, SEE 37 CFR 1.5)	
09/424705	

INTERNATIONAL APPLICATION NO.	INTERNATIONAL FILING DATE	PRIORITY DATE CLAIMED
PCT/DE98/01409	May 22, 1998	May 23, 1997

TITLE OF INVENTION

MUTATED OKT3 ANTIBODY

APPLICANT(S) FOR DO/EO/US

Melvyn LITTLE; Bernard HUBER; Sergey KIPRIYANOV; and Gerhard MOLDENHAUER.

Applicant herewith submits to the United States Designated/Elected Office (DO/EO/US) the following items and other information:

1. ☒ This is a **FIRST** submission of items concerning a filing under 35 U.S.C. 371.
2. ☐ This is a **SECOND** or **SUBSEQUENT** submission of items concerning a filing under 35 U.S.C. 371.
3. ☐ This is an express request to begin national examination procedures (35 U.S.C. 371(f)) at any time rather than delay examination until the expiration of the applicable time limit set in 35 U.S.C. 371(b) and PCT Articles 22 and 39(1).
4. ☒ A proper Demand for International Preliminary Examination was made by the 19th month from the earliest claimed priority date.
5. ☒ A copy of the International Application as filed (35 U.S.C. 371 (c) (2))
   a. ☒ is transmitted herewith (required only if not transmitted by the International Bureau).
   b. ☐ has been transmitted by the International Bureau.
   c. ☐ is not required, as the application was filed in the United States Receiving Office (RO/US).
6. ☒ A translation of the International Application into English (35 U.S.C. 371(c)(2)).
7. ☒ A copy of the International Search Report (PCT/ISA/210).
8. ☐ Amendments to the claims of the International Application under PCT Article 19 (35 U.S.C. 371 (c)(3))
   a. ☐ are transmitted herewith (required only if not transmitted by the International Bureau).
   b. ☐ have been transmitted by the International Bureau.
   c. ☐ have not been made; however, the time limit for making such amendments has NOT expired.
   d. ☐ have not been made and will not be made.
9. ☐ A translation of the amendments to the claims under PCT Article 19 (35 U.S.C. 371(c)(3)).
10. ☐ An oath or declaration of the inventor(s) (35 U.S.C. 371 (c)(4)).
11. ☐ A copy of the International Preliminary Examination Report (PCT/IPEA/409).
12. ☐ A translation of the annexes to the International Preliminary Examination Report under PCT Article 36 (35 U.S.C. 371 (c)(5)).

Items 13 to 18 below concern document(s) or information included:

13. ☐ An Information Disclosure Statement under 37 CFR 1.97 and 1.98.
14. ☐ An assignment document for recording. A separate cover sheet in compliance with 37 CFR 3.28 and 3.31 is included.
15. ☐ A **FIRST** preliminary amendment.
    A **SECOND** or **SUBSEQUENT** preliminary amendment.
16. ☐ A substitute specification.
17. ☐ A change of power of attorney and/or address letter.
18. ☐ Certificate of Mailing by Express Mail
19. ☒ Other items or information:

Amendments to the claims under Article 34 (2 pages); English Translation of the Amendments (2 pages); front cover page of WO98/52975; copy of Chapter 2 demand; and two return post cards.

PCTUS1/REV03

U.S. APPLICATION NO. (IF KNOWN, SEE 37 CFR 1.5)	INTERNATIONAL APPLICATION NO.	ATTORNEY'S DOCKET NUMBER
09/424705	PCT/DE98/01409	35280047US00

20. The following fees are submitted:

BASIC NATIONAL FEE (37 CFR 1.492 (a) (1) - (5)) :		CALCULATIONS PTO USE ONLY
☒ Search Report has been prepared by the EPO or JPO	$840.00	
☐ International preliminary examination fee paid to USPTO (37 CFR 1.482)	$670.00	
☐ No international preliminary examination fee paid to USPTO (37 CFR 1.482) but international search fee paid to USPTO (37 CFR 1.445(a)(2))	$760.00	
☐ Neither international preliminary examination fee (37 CFR 1.482) nor international search fee (37 CFR 1.445(a)(2) paid to USPTO	$970.00	
☐ International preliminary examination fee paid to USPTO (37 CFR 1.482) and all claims satisfied provisions of PCT Article 33(2)-(4)	$96.00	
ENTER APPROPRIATE BASIC FEE AMOUNT =		$840.00
Surcharge of **$130.00** for furnishing the oath or declaration later than ☐ 20 ☐ 30 months from the earliest claimed priority date (37 CFR 1.492 (e)).		$0.00

CLAIMS	NUMBER FILED	NUMBER EXTRA	RATE	
Total claims	12 - 20 =	0	x $18.00	$0.00
Independent claims	1 - 3 =	0	x $78.00	$0.00
Multiple Dependent Claims **(check if applicable)**.			☒	$260.00
TOTAL OF ABOVE CALCULATIONS			=	$1,100.00
Reduction of 1/2 for filing by small entity, if applicable. Verified Small Entity Statement must also be filed (Note 37 CFR 1.9, 1.27, 1.28) **(check if applicable).**			☐	$0.00
SUBTOTAL			=	$1,100.00
Processing fee of **$130.00** for furnishing the English translation later than ☐ 20 ☐ 30 months from the earliest claimed priority date (37 CFR 1.492 (f)).			+	$0.00
TOTAL NATIONAL FEE			=	$1,100.00
Fee for recording the enclosed assignment (37 CFR 1.21(h)). The assignment must be accompanied by an appropriate cover sheet (37 CFR 3.28, 3.31) **(check if applicable).**			☐	$0.00
TOTAL FEES ENCLOSED			=	$1,100.00
Amount to be: refunded				$
charged				$

☒ A check in the amount of **$1,100.00** to cover the above fees is enclosed.

☐ Please charge my Deposit Account No. in the amount of to cover the above fees.
A duplicate copy of this sheet is enclosed.

☒ The Commissioner is hereby authorized to charge any fees which may be required, or credit any overpayment to Deposit Account No. **08-3038** A duplicate copy of this sheet is enclosed.

NOTE: Where an appropriate time limit under 37 CFR 1.494 or 1.495 has not been met, a petition to revive (37 CFR 1.137(a) or (b)) must be filed and granted to restore the application to pending status.

SEND ALL CORRESPONDENCE TO:

Albert P. Halluin
HOWREY & SIMON
BOX 34
1299 Pennsylvania Avenue, N.W.
Washington, D.C. 20004
Telephone (650) 463-8100
Facsimile (650) 463-8400

SIGNATURE

Albert P. Halluin
NAME

25,227
REGISTRATION NUMBER

November 23, 1999
DATE

Mutated OKT3 Antibody

The present invention relates to an H100A position point-mutated OKT3 antibody, a method for the production thereof and its use.

OKT3 is a monoclonal IgG 2a-type antibody originating from mice, which recognizes an epitope of an ε-subunit of the human CD3 complex (Kung et al., Science 206, pp. 347-349 (1979); Van Wauwe et al., J. Immunol. 124, pp. 2708-2713 (1980); Transy et al., Eur. J. Immunol. 19, pp. 947-950 (1989)). The method of obtaining the monoclonal antibody from the corresponding hybridoma is described in detail in these publications. Furthermore, the OKT3-producing hybridoma cell line was deposited by the owner of European patent 0 018 795 under ATCC No. CRL 8001 with the American Type Culture Collection, 12301 Parklawn Drive, Rockville, MD, 20852, on April 26, 1979. OKT3 has been used for a long time to suppress a T-cell response thus preventing the rejection of transplants (Thistlethwaite et al., Transplantation 38, pp. 695-701 (1984); Woodle et al., Transplantation 51, pp. 1207-1212 (1991)). On the other hand, OKT3 can also trigger T-cell activation and proliferation, which stimulates the effector cells, which can be used for the adoptive cancer immunotherapy (Yannelly et al., J. Immunol. Meth. 1, pp. 91-100 (1990)). OKT3 was used as such and as a component of a bispecific antibody to direct cytotoxic T-lymphocytes against tumor cells or virus-infected cells (Nitta et al., Lancet 335, pp. 368-376 (1990); Sanna et al., Bio/Technology 13, pp. 1221-1224 (1995)). Furthermore, humanized versions of the OKT3-monoclonal antibody which were expressed in COS cells are also known (Woodle et al., J. Immunol. 148, pp. 2756-2763 (1992); Adair et al., Human. Antibod. Hybridomas, pp. 41-47 (1994)). So far there has been the problem that OKT3 has no

sufficient stability and particularly cannot be expressed in known recombinant expression systems in stably fashion and sufficient amount.

Therefore, the object of the present invention was to express OKT3 recombinantly and obtain an antibody which has satisfactory stability.

This object is achieved by the subject matters defined in the claims.

The inventors have found that by introducing a point mutation at position H100A of the amino acid sequence of OKT3 the stability increases many times over. This point mutation relates to the exchange of cysteine for another polar amino acid, preferably serine, in the amino acid sequence of OKT3.

For the production of an antibody according to the invention, mRNA from freshly subcloned hybridoma cells of OKT3 is used as a basis. The cDNA is produced according to methods known to a person skilled in the art, which were described in Dübel et al., J. Immunol. Methods 175, pp. 89-95 (1994), for example. The DNA coding for the variable domain of the light chain can be produced by means of PCR using suitable primers, e.g. by means of primers Bi5 and Bi8 which hybridize to the amino-terminal part of the constant domain of the κ-chain and the framework 1 (FR1) region of the variable domain of the κ-chain (Dübel et al., see above). For the amplification of the DNA which codes for the variable domain of the heavy chain, it is possible to use e.g. the primer Bi4 which hybridizes to the amino-terminal part of the constant domain 1 of the γ-chain (Dübel et al., cf. above) and the primer Bi3f which hybridizes to the FR1 region of the heavy chain (Gotter et al., Tumor Targeting 1, pp. 107-114 (1995).

Thereafter, the amplified DNA is inserted in a vector adapted for sequencing and for site specific mutagenesis, as well known to the person skilled in the art. For example, the vector pCR-Skript SK(+) sold by the company of Stratagene can be used. Mutations are inserted in the V_H domain originating from OKT3 by site specific mutagenesis. The person skilled in the art is familiar with the conditions necessary for this purpose, they are also described e.g. in Kunkel et al., Meth. Enzymol. 154, pp. 367-382 (1987). The amino acid substitution at the H100A position of OKT3 (exchange of cysteine) is suitably carried out by using the primer SK1 5'-GTAGTCAAGGCTGTAATGATCATC if an exchange for serine shall be carried out at this position.

Then, the thus modified DNA can be cloned into a vector and expression vector, respectively. The person skilled in the art is familiar with examples thereof. In the case of an expression vector, these are pGEMEX, pUC derivatives or pET3b. For the expression in yeast, e.g. pY100 and Ycpad1 have to be mentioned while e.g. pKCR, pEFBOS, cDM8 and pCEV4 have to be indicated for the expression in animal cells. The baculovirus expression vector pAcSGHisNT-1 is especially suitable for the expression in insect cells. The expression in *E. coli* is preferred according to the invention, for which purpose preferably the vector pHOG21 shown in figure 1 (Kipriyanov et al., J. Immunol. Methods 196, pp. 51-62 (1996) is used, in which the mutated OKT3 single chain (ScFv) gene is inserted as NcoI/BamHI DNA fragment. A single-chain antibody OKT3 mutated at position 100 A (Kabat numbering system) is expressed, which has the sequence shown in figure 2.

The person skilled in the art is familiar with cells adapted to express a DNA which is present in an expression vector. Examples of such cells comprise the *E. coli* strains HB101, DH1, x1776, JM101, JM109, BI21 and SG13009, the yeast strain *Saccharomyces cerevisiae* and the animal cells 3T3, FM3A,

CHO, COS, Vero and HeLa as well as the insect cells sf9. The use of the XL1-Blue *E. coli* cells sold by the company of Stratagene is preferred.

The person skilled in the art knows in which way a DNA has to be inserted in an expression vector. He is also familiar with the fact that this DNA can be inserted in combination with a DNA coding for another protein and peptide, respectively, so that the DNA can be expressed in the form of a fusion protein, e.g. in the form of a His fusion protein. The information necessary for this purpose is included in the preferably used plasmid pHOG21. Furthermore, the mutated form of OKT3 can be present in the form of a bispecific antibody, e.g. in combination with an antibody against human CD19 complex. The sequence of such a bispecific antibody is shown in figure 3.

Antibodies according to the invention distinguish themselves in that they can be produced by means of recombinant methods in sufficient amount and have a stability greater as compared to the non-mutated monoclonal antibody OKT3. This stability expresses itself e.g. in that the mutated antibody has lost almost nothing of its original binding affinity even after one month of storage at 4°C in PBS, whereas OKT3 has markedly lost binding affinity under these conditions (46 %). In addition, the antibody according to the invention has the advantage that as a single-chain antibody (scFv) it has faster blood clearance and better tumor penetration. Furthermore, ScFvs are very useful molecules to transport pharmacons, toxins or radionuclides to tumor sites, which is important for tumor diagnosis and tumor treatment.

The present invention is further described by means of the figures.

Figure 1: plasmid pHOG21
the abbreviations used therein having the following meanings:
Ap^R: ampicillin resistance gene

c-myc: sequence coding for an epitope which is recognized by the monoclonal antibody 9E10 (Cambridge Research Biochemicals, Cambridge, Great Britain)

ColE1: origin of DNA replication

f1 IG: intergenic region of the f1 phage

His_6: sequence coding for 6 histidine residues

linker: sequence coding for 17 amino acids which links the V_H and V_L domains

pelB: signal peptide sequence for bacterial pectate lyase

P/O: wild type lac promoter / operator

Figure 2: Nucleotide sequence and derived amino acid sequence of the mutated OKT3 single-chain antibody

Figure 3: bispecific antibody composed of mutated OKT3 and anti-CD19

The invention is explained in more detail by the example.

EXAMPLE 1: Preparation of an antibody according to the invention

The isolation of mRNA from freshly subcloned hybridoma cells of OKT3 and the cDNA synthesis were carried out as described in "Dübel et al., J. Immunol. Methods 175, pp. 89-95 (1994)". The DNA coding for the variable domain of the light chain was produced by means of PCR using the primers Bi5 and Bi8 which hybridize to the amino-terminal part of the constant domain of the κ-chain and the framework 1 (FR1) region of the variable domain of the κ-chain (Dübel et al., cf. above). The primer Bi4, which hybridizes to the amino-terminal part of the constant domain 1 of the γ-chain (Dübel et al., cf. above), and the primer Bi3f, which hybridizes to the FR1 region of the heavy chain (Gotter et al., Tumor

Targeting 1, pp. 107-114 (1995), were used for the amplification of the DNA which codes for the variable domain of the heavy chain. The 50 µl reaction mixture contained 10 pmol of each primer and 50 ng hybridoma cDNA, 100 µM of each of the dNTPs, 1 x vent buffer (Boehringer Mannheim), 5 µg BSA and 1 U Vent DNA polymerase. 30 cycles were carried out per 1 minute at 95°, 1 min. at 55°C and 2 minutes at 75°C in a PCR thermocycler. The amplified DNA was purified with a QIA quick PCR purification kit (Qiagen, Hilden).

Thereafter, the amplified DNA was 'blunt-end' ligated into the vector pCR-Skript SK(+) sold by the company of Stratagene, which had been cleaved using the SrfI restriction enzyme. Mutations were inserted in the V_H domain originating from OKT3 by site specific mutagenesis (Kunkel et al., Meth. Enzymol. 154, pp. 367-382 (1987)). The amino acid substitution at position H100A of OKT3 (exchange of cysteine for serine) was carried out using the primer SK1 5'-GTAGTCAAGGCTGTAATGATCATC.

For the expression of the resulting mutated DNA the vector pHOG21 shown in figure 1 (Kipriyanov et al., J. Immunol. Methods 196, pp. 51-62 (1996) was used, in which the mutated OKT3 single chain (scFv) gene is inserted as NcoI/BamHI DNA fragment. XL1-Blue *E. coli* cells (Stratagene) were transformed with this expression vector and allowed to grow in a 2xYT medium having 50 µg/ml ampicillin and 100 mM glucose ($2xYT_{GA}$) at 37°C overnight. Dilutions (1:50) of the overnight cultures in $2xYT_{GA}$ were allowed to grow at 37°C with shaking at 37°C. As soon as the cultures had reached OD_{600} = 0.8, the bacteria were pelleted by centrifugation at 1500 g and 20°C for 10 minutes and resuspended in the same volume of fresh 2xYT medium containing 50 µg/ml ampicillin and 0.4 M sucrose. IPTG was added up to a final concentration of 0.1 mM and the growth was continued at room temperature for 20 hours. The cells were collected by centrifugation at 5000 g and 4°C for 10 minutes. The supernatant of the culture was stored on ice. In order to isolate soluble periplasmic proteins, the pelleted bacteria

were taken up in ice-cold 50 mM Tris-HCl, 20 % sucrose, 1 mM EDTA, pH 8.0 (5 % of the original volume). After one hour of incubation on ice accompanied by occasional stirring, spheroplasts were centrifuged off at 30,000 g and 4°C for 30 minutes, the soluble periplasmic extract occurring as supernatant and the spheroplasts plus insoluble periplasmic material occurring as pellet. The above supernatant of the culture stored on ice and the soluble periplasmic extract were combined and clarified by an additional centrifugation (30,000 g, 4°C, 40 min.). Following filtration by glass filters having a pore size of 10 to 16 μm and then 0.2 μm, the volume became 10 times as high by concentration with Amicon YM10 membranes (Amicon company, Witten). The concentrated supernatant was clarified by centrifugation and dialyzed against 50 mM Tris-HCl, 1 M NaCl, pH 7.0 at 4°C. Immobilized metal affinity chromatography (IMAC) was charged with Ni^{2+} at 4°C using a 5 ml column of chelatizing sepharose (Pharmacia company) and equilibrated with 50 mM Tris-HCl, 1 M NaCl, pH 7.0 (start buffer). Material adsorbed on the column was eluted using 50 mM Tris-HCl, 1 M NaCl, 250 mM imidazole, pH 7.0. Having changed the buffer to 50 mM MES, pH 6.0, the protein was further purified on a mono S ion exchange column (Pharmacia). The purified scFv antibody according to the invention was dialyzed in PBS (15 mM sodium phosphate, 0.15 M NaCl, pH 7.4). For a relatively long storage, the antibody was frozen in the presence of BSA (final concentration 10 mg/ml) and stored at -80°C.

Claims

1) A monoclonal antibody, characterized by an exchange of cysteine for another polar amino acid at position H100A of the OKT3 antibody known under this name.

2) The monoclonal antibody, characterized in that the polar amino acid is serine.

3) The monoclonal antibody according to claim 1 or 2, characterized in that it includes the sequence indicated in figure 2.

4) A method for the production of the monoclonal antibody according to any one of claims 1 to 3, characterized by the steps of:

   a) obtainment of mRNA from freshly subcloned hybridoma cells of OKT3 and transcription into cDNA,

   b) amplification of the DNA coding for the variable domains of the light and heavy chains by means of PCR using suitable primers,

   c) cloning of the DNA obtained in b) into a vector adapted for site-specific mutagenesis as well as introduction of the desired mutation using suitable primers,

   d) insertion of the mutated DNA obtained in c) in an expression vector and expression in a suitable expression system.

5) The method according to claim 4, wherein the primers used in step b) are Bi5, Bi8, Bi4 and Bi3f.

6) The method according to claim 4 or 5, wherein the vector used in step c) is pCR-Skript SK(+).

7) The method according to any one of claims 4 to 6, wherein the primer SK1 5'-GTAGTCAAGGCTGTAATGATCATC is used in step c).

8) The method according to any one of claims 4 to 7, wherein the expression vector used in step d) is pHOG21.

9) The method according to any one of claims 4 to 8, wherein the expression takes place in XL1-Blue *E. coli* cells.

10) Use of the monoclonal antibody according to any one of claims 1 to 3 for reducing or eliminating a transplant rejection by an organ transplant recipient.

11) Use of the monoclonal antibody according to any one of claims 1 to 3 for tumor diagnosis or tumor treatment.

Abstract of the Disclosure

The invention relates to an H100A position point-mutated OKT3 antibody, a method for the production and use thereof.

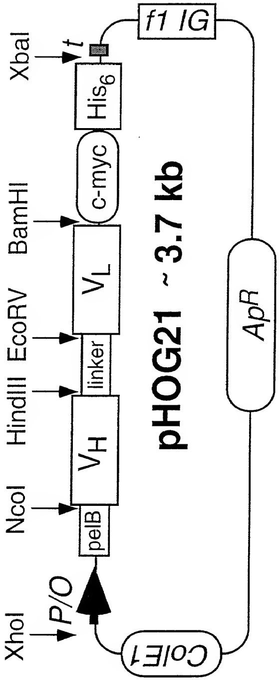

Fig. 1

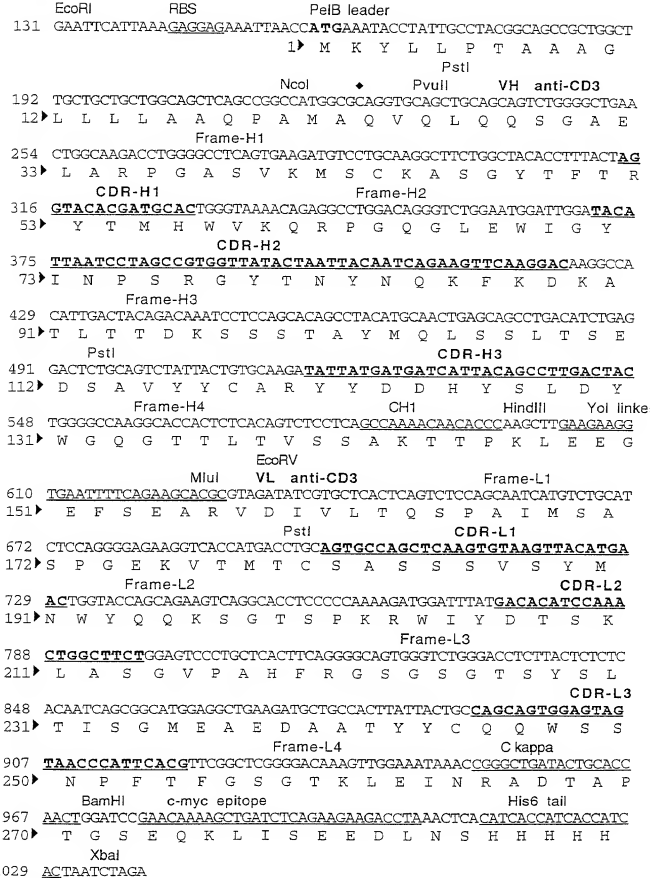

Fig. 2

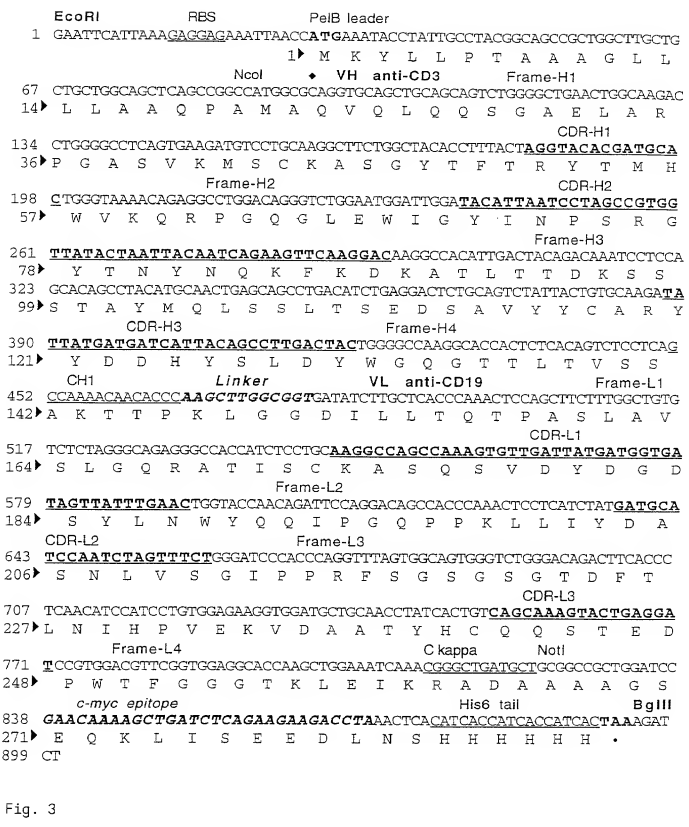
EcoRI
RBS
PelB leader
NcoI
VH anti-CD3
Frame-H1
CDR-H1
Frame-H2
CDR-H2
Frame-H3
CDR-H3
Frame-H4
CH1
Linker
VL anti-CD19
Frame-L1
CDR-L1
Frame-L2
CDR-L2
Frame-L3
CDR-L3
Frame-L4
C kappa
NotI
c-myc epitope
His6 tail
BglII

Fig. 3

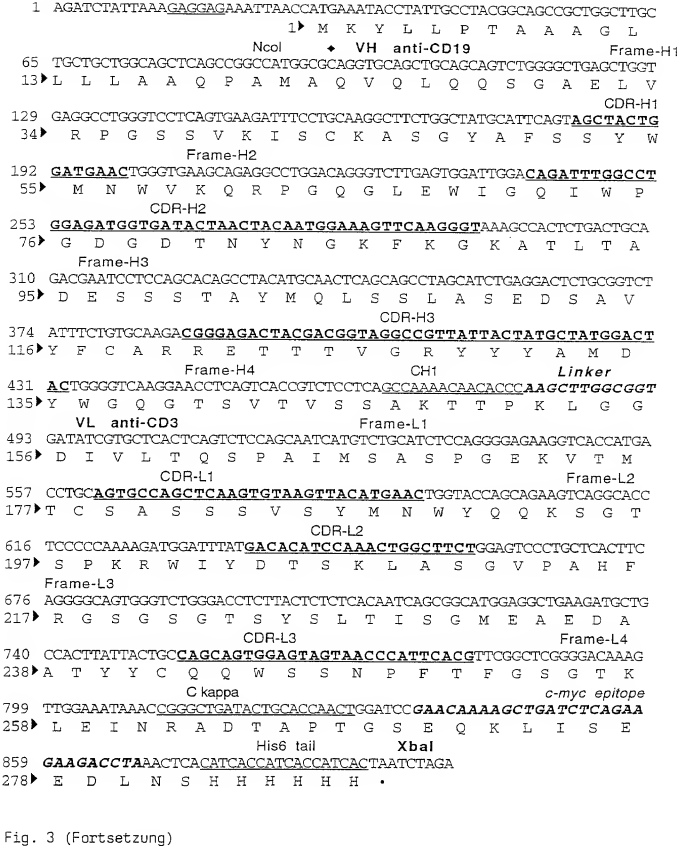

Fig. 3 (Fortsetzung)

(line 1-17, page 1)

REGISTERED UTILITY MODEL GAZETTE

Registration No. 3034512

Published on: February 25, 1997 Registered on: November 27, 1996

Appln. No. Hei. 8 – 8720

Filed on: August 8, 1996

Inventor / Applicant: Takeshi Nakasuji

Title of Device: **PORTABLE COMMUNICATION TERMINAL WITH ORNAMENT**

(line 30-39, right column, page 2)

[REFERENCE NUMERALS]

1 .... Portable communication terminal with ornament,

2 .... Display, 3 .... Lustrous color stones,

4 .... Outer surface, 5 .... Members for displaying initials,

6 .... Plate, 7 .... Lid,

8 .... Photography, 'D' ....Main body

(paragraph 0007, page 8)

[0007]

In Fig.1 and Fig.2, 1 denotes the portable communication terminal with ornament. Lustrous colored stones 3 are attached to the periphery of display 2 of the terminal 1.

The lustrous colored stones 3 are, for example, "mirror stones" made of acrylic plastic, colored stones made by cutting colored or transparent glass, "dia-lanes" (ornaments made by linking cut-glasses trochally like diamonds), semiprecious stones, or artificial pearl.

The lustrous colored stones 3 may be attached to the periphery of display 2 by precedently polishing the surface of the periphery and applying adhesives on the surface.

The adhesives are, for example, vinyl acetate adhesives such as vinyl acetate resin emulsion, artificial gum adhesives, epoxy resin adhesives, or cyanoacrylate adhesives. Luminous or fluorescent paints may be mixed with the adhesives.

Coating may be carried out on surface of the lustrous colored stones 3 using "clear paints" made of acrylic or epoxy resins.

As substitute for a part of the lustrous colored stones 3, molded artificial resin, punched artificial resin, molded metal, or punched metal in the shape of animals, plants, flowers, stars, moon, geometric configurations, abstract shapes, or dolls may be used.

Combined Declaration and Power of Attorney for Patent Application

Docket Number: 35280047US00

As a below named inventor, I hereby declare that:

My residence, post office address and citizenship are as stated below next to my name.

I believe I am an original and joint inventor of the subject matter that is claimed and for which a patent is sought on the invention entitled , the specification of which is attached hereto unless the following box is checked:

☒ was filed on **November 23, 1999**;
as United States Application Number **09/424,705**.

I hereby state that I have reviewed and understand the contents of the above identified specification, including the claims, as amended by any amendment referred to above.

I acknowledge the duty to disclose information that is material to patentability as defined in 37 C.F.R. § 1.56.

I hereby claim foreign priority benefits under 35 U.S.C. § 119(a)-(d) or § 365(b) of any foreign application(s) for patent or inventor's certificate, or § 365(a) of any PCT international application, which designated at least one country other than the United States listed below, and have also identified below any foreign application for patent or inventor's certificate, or PCT international application having a filing date before that of the application on which priority is claimed.

PRIOR FOREIGN APPLICATION(S)

Application No.	Country	(Day/Month/Year/Filed)	Priority Claimed
197 21 700.1	Germany	23 May 1997	✖ Yes No
PCT/DE9801409	WO	22 May 1998	✖ Yes No
			Yes No
			Yes No

I hereby claim the benefit under 35 U.S.C. §119(e) of any United States provisional application(s) listed below.

Application No.	Filing Date

I hereby claim the benefit under 35 U.S.C. § 120 of any United States application(s), or under § 365(c) of any PCT international application designating the United States, listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States or PCT international application in the manner provided by the first paragraph of 35 U.S.C. § 112, I acknowledge the duty to disclose information that is material to patentability as defined in 37 C.F.R. § 1.56 that became available between the filing date of the prior application and the national or PCT international filing date of this application.

Application No.	Filing Date	(Status – patented, pending, abandoned)

I hereby appoint the following attorney(s) and/or agent(s) to prosecute this application and to transact all business in the Patent and Trademark Office connected therewith:

Robert A. Auchter, Reg. No. 38,069
Jeffrey I. Auerbach, Reg. No. 32,680
William D. Belanger, Reg. No. 40,509
Michael J. Bell, Reg. No. 39,604
John A. Bendrick, Reg. No. 41,612
Celine T. Callahan, Reg. No. 34,301
Cono A. Carrano, Reg. No. 39,623
Jenny W. Chen, Reg. No. 44,604
June E. Cohan, Reg. No. 43,741
Joseph V. Colaianni, Reg. No. 39,948
Chris Comuntzis, Reg. No. 31,097
Mary S. Consalvi, Reg. No. 32,212
Ben M. Davidson, Reg. No. 38,424
Ross E. Davidson, Reg. No. 41,698
James F. Davis, Reg. No. 21,077
Thomas M. Dunham, Reg. No. 39,965
Thomas C. Fiala, Reg. No. 43,610
Joel Mark Freed, Reg. No. 25,101
Alan M. Grimaldi, Reg. No. 26,599
Albert P. Halluin, Reg. No. 25,227
Leslie L. Jacobs, Jr., Reg. No. 40,659
Derek J. Jardieu, Reg. No. 44,483
Christopher L. Kelley, Reg. No. 42,714
Brian S. Y. Kim, Reg. No. 41,114
Richard H. Kjeldgaard, Reg. No. 30,186
Andrew R. Kopsidas, Reg. No. 42,759
David J. Kulik, Reg. No. 36,576
Viola T. Kung, Reg. No. 41,131
Robert C. Laurenson, Reg. No. 34,206
Joseph P. Lavelle, Reg. No. 31,046
Don F. Livornese, Reg. No. 32,040
David R. Marsh, Reg. No. 41,408
Christopher A. Mathews, Reg. No. 35,944
Joseph A. Micallef, Reg. No. 39,772
Andrew Y. Platnicia, Reg. No. 40,772
Andrea G. Reister, Reg. No. 36,253
Timothy W. Riffe, Reg. No. 43,881
Stephen J. Rosenman, Reg. No. 29,209
Richard M. San Pietro, Reg. No. 45,071
Anthony W. Shaw, Reg. No. 30,104
J. David Smith, Reg. No. 39,839
Michael J. Songer, Reg. No. 39,841
Jennifer A. Tipsord, Reg. No. 40,205
William K. West, Reg. No. 22,457
Adam K. Whiting, Reg. No. 44,400
Karen W. Wong, Reg. No. 44,409
Robert J. Worrall, Reg. No. 37,969
Wallace Wu, Reg. No. 45,380

Send Correspondence to:

Albert P. Halluin
HOWREY SIMON ARNOLD & WHITE, LLP
Box No. 34
1299 Pennsylvania Avenue, N.W.
Washington, D.C. 20004-2402
Facsimile: (202) 383-7195

Direct Telephone Calls to: (202) 783-0800

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

FULL NAME OF FIRST INVENTOR: LITTLE, Melvyn	**CITIZENSHIP:** BRITISH
RESIDENCE: FRITZ-VON BRIESEN-STR. 10, 69151 NECKARGMÜND, GERMANY	**DATE:** 8.5.00
POST OFFICE ADDRESS: SAME AS ABOVE	**INVENTOR'S SIGNATURE:**
FULL NAME OF SECOND INVENTOR: KIPRIYANOV, Sergey	**CITIZENSHIP:** RUSSIAN
RESIDENCE: FURTWÄNGLERSTR.3 69121 HEIDELBERG, GERMANY	**DATE:** 8.05.00
POST OFFICE ADDRESS: SAME AS ABOVE	**INVENTOR'S SIGNATURE:**
FULL NAME OF THIRD INVENTOR: MOLDENHAUER, Gerhard	**CITIZENSHIP:** GERMAN
RESIDENCE: BRÜCKENSTR. 41 69120 HEIDELBERG, GERMANY	**DATE:** 9.5.00
POST OFFICE ADDRESS: SAME AS ABOVE	**INVENTOR'S SIGNATURE:** J. Moldenhauer